

### **REMARKS**

This Amendment is being filed in response to the Office Action mailed from the U.S. Patent and Trademark Office on March 22, 2004. Claims 1-11 and 14 were previously canceled. Claims 12, 13 and 15-19 will be pending upon entry of this Amendment. Applicants respectfully request reconsideration and allowance of the pending claims.

#### **Priority Documents**

The Office Action Summary (Paper No. 03172004) indicates that certified copies of the priority documents have not been received. Applicants' representatives are in the process of obtaining the required certified copies from a foreign patent office, and will forward them as soon as they are received.

#### **Claim Amendments**

Claim 12 has been amended to delete the word "general" before "formula" in the second line, to delete erroneous punctuation in line 8, to replace "of said compounds" with "compound of formula (I)" in line 10, and to add "in need thereof" after "mammal" in line 11.

Claim 15 has been amended to recite the listed diseases in the singular, as requested by the Examiner.

Claim 16 has been amended to add "each independently" before "a straight-chain" and to remove "each" at the end of the claim. Support for the new wording of claim 16 is found in the specification, for example, at page 2, line 7.

These amendments merely clarify that which applicants regard as the invention and do not introduce any new matter.

#### **Rejection of claims 12 and 16-19 under 35 U.S.C. §112, first paragraph**

Claims 12 and 16-19 are rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement.

The Examiner states at page 2 of Paper No. 03172004 that “The specification, while being enabling for the specific cancers disclosed on page 25, lines 2-3, does not reasonably provide enablement for any and all cancers.” Applicants respectfully traverse the rejection.

Following an interview with the previous Examiner in this case, Applicants amended claim 12 to recite a method of treating cancerous disease “sensitive to the preparation of claim 1” (now corresponding to “sensitive to a compound of formula (I)”). See Amendment filed July 8, 2003. Thus, amended claim 12 does not read on a method of treating “any and all cancers” as alleged in the instant Office Action. Nor does the claimed invention require undue experimentation to determine which cancers are treatable with a compound of formula (I), because the thioplatin compounds of claim 12 are widely effective against a variety of cancers, including solid tumors generally and blood-born tumors such as leukemias. “Another advantage of the compounds according to the invention is that they have a broad activity spectrum against the most varying tumors and are particularly also effective against tumors which have resisted treatment with platinum compounds (e.g. cisplatin) so far.” Specification at page 5, lines 14 (leukemias) and 20-25. The cisplatins, a group of anticancer agents which are chemically related to the compounds recited in claim 12, are well known for their effectiveness against a wide variety of tumors. *See, e.g.,* Z.H. Siddik, *Oncogene* 22:7265 (2003); a copy of the abstract is enclosed as Exhibit A. Siddik states at the beginning of the Abstract, “Cisplatin is one of the most potent antitumor agents known, displaying clinical activity against a wide variety of solid tumors.”

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of claims 12-13 and 15-19 under 35 U.S.C. §112, second paragraph

Claims 12-13 and 15-19 are rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness.

Applicants respectfully traverse the rejection.

In response to the Examiner’s suggestions at pages 5 and 6, Applicants have made the following amendments.

The phrase “cancerous disease” in claim 12 has been amended to recite “a cancerous disease”.

The term “general” has been deleted from claim 12.

The period at line 8 of claim 12 has been deleted.

In claim 12, the phrase “said compounds” has been amended to recite “compound of formula (I)”.

Claim 12 has been amended to include the phrase “comprising administering to said human being or mammal in need thereof a pharmaceutical preparation. . .”

Claim 15 has been amended to recite the listed diseases in the singular, as requested by the Examiner.

Claim 16 has been amended to replace the phrase “R<sub>1</sub> and R<sub>2</sub> are a straight-chain” with the phrase “R<sub>1</sub> and R<sub>2</sub> are each independently a straight chain.”

In view of the above, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph rejection of claims 12-13 and 15-19.

Rejection of claims 12 and 16-19 under 35 U.S.C. §102(b)

Claims 12 and 16-19 are rejected under 35 U.S.C. §102(b) for alleged lack of novelty in view of Osa et al. (1986, Chem Pharm Bull, 34:3563).

The Examiner states at page 6,

Osa ...discloses the instant compound when R<sub>1</sub> and R<sub>2</sub> are each ethyl and that it has high antitumor activity. Claims 13 and 19 appear to differ over Osa in reciting a pharmaceutical composition and a compatible inert carrier or diluent. However, it would be inherent that the compound of Osa was administered as a composition, since it would have been administered as a solution.

Applicants respectfully traverse the rejection.

For a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Although the Osa et al. reference describes a compound of the formula recited in claim 12 (Compound 56, see Table VI, page 3569), the Osa et al. reference does not teach using this compound for a method of treating a cancerous disease wherein the cancerous disease is sensitive to the compound. In fact, the Osa reference does not teach or even imply that compound 56 has antitumor activity. No results for that compound appear in Table VII of Osa. Osa teaches that “three synthesized *cis*-dichloroplatinum(II) complexes coordinating di(3-methylpyridine), di(quinoline) and di(isoquinoline) and a polynuclear platinum piperidine complex (Pt<sub>4</sub>Cl<sub>5</sub>(OH)<sub>3</sub>(C<sub>3</sub>H<sub>11</sub>N)<sub>6</sub>3H<sub>2</sub>O) had high antitumor activities against Sarcoma 180 ascites in female ICR/CRJ mice.” (see abstract). The Osa et al. reference also states at page 3571, “[t]he antitumor activities of the synthesized Pt complexes...are listed in Table VII. The complexes Nos. 8, 19, 27 and 48 had high antitumor activities.”

In view of the above, the Osa et al. reference does not teach “a method of treating a cancerous disease sensitive to a compound of formula (I).” Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of claims 12-13 and 15-19 under 35 U.S.C. §103(a)

Claims 12-13 and 15-19 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over the Osa et al. reference in view of MEDLINE AN 96354887(Shibusawa) or MEDLINE AN 1998252553 (Weisman) or MEDLINE AN 1998277308 (Tessier) or MEDLINE AN 90112359 (Hollis).

The Examiner states at page 7, “[c]laims 13 and 15 differ over Osa in reciting specific tumors. However, Shibusawa (abstract), Weisman (abstract) and Tessier (abstract) disclose that the platinum compound cisplatin is useful to treat colorectal carcinoma, squamous cell cancer of the head and neck and melanoma. . . Furthermore, Hollis (abstract) discloses that cisplatin has antitumor activity against Sarcoma 180 ascites. It would be obvious to one of ordinary skill in the art that the instant compound would be effective in treating the tumors of claims 13 and 15,

since both it and cisplatin are effective against Sarcoma 180 ascites and cisplatin is taught to be useful to treat the recited tumors of claims 13 and 15.” Applicants respectfully traverse the rejection.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). Osa does not teach or suggest an antitumor activity of a compound of formula (I). Thus, even if the references are combined, they do not provide the invention as claimed. The teachings of Shibusawa, Weisman, and Tessier on cisplatin do not remedy the defects of Osa. It follows furthermore that, lacking any indication of antitumor activity, there would be no motivation to combine the references or any expectation of success based on their combined teachings.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §103(a) rejection of claims 12-13 and 15-19.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants’ attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

Date:

July 22, 2004

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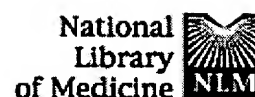
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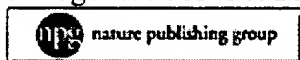
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## Cisplatin: mode of cytotoxic action and molecular basis of resistance.

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Cisplatin is one of the most potent antitumor agents known, displaying clinic activity against a wide variety of solid tumors. Its cytotoxic mode of action is mediated by its interaction with DNA to form DNA adducts, primarily intrastrand crosslink adducts, which activate several signal transduction pathways, including those involving ATR, p53, p73, and MAPK, and culminate in the activation of apoptosis. DNA damage-mediated apoptotic signals, however, can be attenuated, and the resistance that ensues is a major limitation of cisplatin-based chemotherapy. The mechanisms responsible for cisplatin resistance are several, and contribute to the multifactorial nature of the problem. Resistance mechanisms that limit the extent of DNA damage include reduced drug uptake, increased drug inactivation, and increased DNA adduct repair. Origins of these pharmacologic-based mechanisms, however, are at the molecular level. Mechanisms that inhibit propagation of the DNA damage signal to the apoptotic machinery include loss of damage recognition overexpression of HER-2/neu, activation of the PI3-K/Akt (also known as PI3-K/PKB) pathway, loss of p53 function, overexpression of antiapoptotic bcl-2, and interference in caspase activation. The molecular signature defining the resistant phenotype varies between tumors, and the number of resistance mechanisms activated in response to selection pressures dictates the overall extent of cisplatin resistance.

Publication Types:

- Review
- Review, Academic

PMID: 14576837 [PubMed - indexed for MEDLINE]